

**NOVEL DAMMARANE SAPOGENINS,
THEIR USE AS ANTI-CANCER AGENTS,
AND A PROCESS FOR PRODUCING SAME**

5 This is a continuation-in-part of application Serial No. 09/910,887, filed
July 24, 2001.

FIELD OF THE INVENTION

10 **[0001]** This invention relates to novel dammarane sapogenins, their use in anti-
cancer applications, and a process of producing the dammarane sapogenins. More
particularly, the invention pertains to a novel group of dammarane sapogenins
obtained by chemical cleavage of dammarane saponins extracted from panax
15 ginseng, panax quinquefol, panax notoginseng and other species in the ginseng
family, and a novel preparation of anticancer agent containing one or more of these
novel sapogenins for the treatment of cancer, particularly multi-drug resistant
cancers, as well as a process for producing these novel sapogenins.

BACKGROUND OF INVENTION AND RELATED ART

20 **[0002]** Since the beginning of the last decade, anti-cancer research has been
increasingly directed to the discovery of novel anti-cancer agents obtained from
natural sources, as well as identifying and preparing synthetic compounds found in
natural sources.

25 **[0003]** Ginseng saponins (dammarane saponins, also called "ginsenosides", which
are effective ingredients that organically exist in panax ginseng, panax quinquefol,
panax notoginseng and other species in the ginseng family) and sapogenins (those
that do not naturally exist in the ginseng plant or other species in the ginseng family
30 and can be derived only through chemical structure modification by cleavage and/or
semi-synthesis of dammarane saponins), as natural-source root compounds, have
been broadly researched for their anti-cancer characteristics. Some of them have
been reported to have anti-cancer effects, of which, for example, ginsenoside Rh2
[3-O- β -D-glucopyranosyl-20(s)- protopanaxadiol] has been reported for its anti-
35 cancer activities [1], including induction of differentiation and apoptosis in cancer
cells [5-11], inhibition of the growth of human ovarian cancer in nude mice after
oral administration [9], and the ability to inhibit the multiplication of multi-drug
resistance (MDR) cancer cells while used with other chemotherapy drugs in vitro
[12].

[0004] Ginsenoside Rg3 [3-O-[β-D-glucopyranosyl(1→2)-β-D-glucopyranosyl]-20(s)- protopanaxadiol] has been reported to inhibit the invasion by various cancer cells [13] and suppress the proliferation of human prostate cancer cells [14] in vitro, and to inhibit lung metastasis in mice [15] and peritoneal metastasis in rats [16].

[0005] A metabolite of ginseng saponin produced by human intestinal bacteria, Mc [20-O-[α-L-arabinofuranosyl (1→6)-β-D-glucopyranosyl]-20(s)-protopanaxadiol], has been reported to inhibit the vascularization of tumors and extravasation of cancer cells [17].

[0006] While conventional chemotherapy agents directly attack the cancer cells and exhibit severe adverse side effects, some ginseng saponins and sapogenins, as well as their intestinal bacteria metabolites, have been reported to have inhibitory effects on cancers by induction of cancer-cell apoptosis and /or by suppression of vascularization of cancers with few adverse side effects.

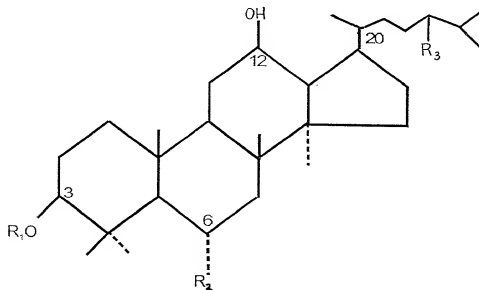
[0007] In the case of treatment of cancers with ginseng saponins, it has been reported that saponins which are metabolized to sapogenins by intestinal bacteria have anti-cancer effects. It has also been reported that ginseng saponins with a hydroxyl at C-20(R), or 20(R) epimers, such as 20(R)-Rh2 and 20(R)-Rg3 have much lower biological activities than those with a hydroxyl at C-20(S), or 20(S) epimers, such as 20(S)-Rh2 and 20(S)-Rg3 respectively. Currently, mixtures of 20(R) and 20(S) epimers are very difficult if not impossible to separate. Thus the mixture has lower efficacy than that of 20(S) epimer. Furthermore, all previously discovered ginsenosides and sapogenins either have sugar moieties at C-3, C-6 or C-20, or have a hydroxyl at C-20, or have both.

SUMMARY OF THE INVENTION

[0008] This invention relates to a group of novel sapogenins, their use in anti-cancer applications, and to a process for their production. More particularly, this invention pertains to a novel group of dammarane sapogenins, PAM-120, PBM-110 and PBM-100 (the dammarance sapogenine structure in these three sapogenins is specifically clean of any sugar moieties (glycons) at any position and a hydroxyl at C-20) and PAN-20 and PAN-30 (the dammarance sapogenin structure has sugar moieties (glycons) but is free of hydroxyl at C-20), obtained by chemical cleavage

of dammarane saponins. The invention also includes a novel application of the said sapogenins for anti-cancer treatment by using them separately or together, and/or jointly with other drugs, as well as to the process of producing these novel sapogenins. Said novel dammarane sapogenins show surprising anti-cancer effect when applied. In particular, the novel dammarane sapogenins show unexpected and superior activity against multi-drug resistant cancers.

[0009] The invention is directed to a sapogenin according to the formula:



wherein R₁ is H, glc or glc¹⁻² glc, R₂ is H or OH, R₃ is H or OH; and when R₁, R₂ and R₃ are H, there are double bonds at positions 20(21) and 24(25); and when R₁ is H, R₂ is OH and R₃ is OH, there are double bonds at positions 20(22) and 25(26); and when R₁ is H, R₂ is OH and R₃ is H, there are double bonds at positions 20(22) and 24(25); and when R₁ is glc, R₂ is H and R₃ is H, there are double bonds at positions 20(21) and 24(25); and when R₁ is glc¹⁻²glc, R₂ is H and R₃ is H, there are double bonds at positions 20(22) and 24(25); and pharmaceutically acceptable compositions incorporating said sapogenins.

[0010] The invention in one embodiment is directed to a sapogenin according to the formula: